REMARKS

At the outset, Applicants would like to thank the Examiner for the courtesy of the personal Examiner's interview conducted with Applicants' representatives on January 7, 2004, during which the claims in the above-referenced application were discussed.

Applicants note that the Amendments filed May 28, 2003 and August 7, 2003 have been entered.

Claims 50, 53, and 57-58 were pending in the above-referenced application.

I. Amendments to the Claims

Claims 50, 53 and 57-58 have been canceled without prejudice or disclaimer of the subject matter contained therein. Applicants reserve the right to pursue the subject matter of the canceled claims in this or future related applications.

Claims 60-76 have been newly added. Support for the newly added claims can be found throughout the specification as filed. Specifically, support for the newly added claims can be found at page 2, ll. 9-38 continuing on page 3, ll. 1-10 and ll. 15-17; page 7, ll. 2-6; page 8, ll. 12-20; page 9, ll. 5-8; page 16, ll. 20-22; p.21, ll. 3-9; p.22, ll. 7-14; page 23, ll. 4-9; page 24, ll. 4-11 and ll. 22-36; page 33, ll. 7-14; and Example 17. It is submitted that no new matter has been added.

II. Rejections under 35 U.S.C. § 102(e)

Applicants gratefully acknowledge that the previous rejection of the claims under 35 U.S.C. § 102(e), for allegedly being anticipated by Ledbetter et al. (U.S. Patent No. 6,010,902), has been withdrawn, because the Examiner deemed the referenced

heteroconjugates or bispecific antibodies to be distinguishable from the claimed antibodies covalently attached to a surface (Office Action, page 2, paragraph 4).

III. Rejections under 35 U.S.C. § 103

Claims 50, 53 and 57-58 stand rejected under 35 U.S.C. § 103 as being unpatentable over Ledbetter et al. (EP0440373) in view of Ledbetter et al. (U.S. Patent No.: 6,010,902) and Chang (U.S. Patent No.: 6,129,916) (Office Action, page 2, paragraph 5).

With the cancellation of claims 50, 53 and 57-58, this rejection as it applies to these claims has been rendered moot. Thus, Applicants address this rejection as it potentially applies to newly added claims 60-76.

The Examiner relies on Ledbetter et al. (EP0440373) to teach "methods of activating T lymphocytes with immobilized anti-CD3 and immobilized anti-CD28 antibodies." The Examiner admits that "Ledbetter et al. differ from the claimed methods by not exemplifying combining anti-CD28 and anti-CD3 antibodies on the same plate," but alleges that "Ledbetter et al. do teach combining both specificities to stimulate T cells and to immobilize both antibodies on plastic surfaces" (Office Action, page 3, first and second paragraphs).

The Examiner relies on Ledbetter et al. (U.S. Patent No.: 6,010,902) to teach "stimulating T cells with the combination of antibodies to CD3 and anti-CD28 antibodies (e.g. 9.3) in order to stimulate T cell populations and subpopulations and reinfused in patients (e.g. see columns 15-16) (see entire document, including Detailed Description of the Invention and Examples)" and for teaching that "these cell populations have increased signal transduction, which can be measured by various known assays" (Office Action, page 3, last paragraph).

The Examiner relies on Chang (U.S. Patent No.: 6,129,916) to teach "combining the particular CD3 and CD28 specificities, by teaching the use of microbeads and cross-linking by well-established manner (columns 7-8) in cross-linking anti-CD3 and anti-CD28 antibodies on microbeads to activate T cells *in vivo*" (Office Action, page 4, third paragraph). The Examiner alleges that although Chang focuses on the *in vivo* administration of stimulating immunoconjugates, "it was known to stimulate T cells *in vitro* via immobilized stimuli" and further, that "both Ledbetter et al. references teach stimulating T cells for adoptive immunotherapy via CD3 and CD28 stimulation" (Office Action, page 4, fourth paragraph).

Finally, the Examiner alleges that "it was an art known practice to monitor cell proliferation of interest, including cell size and cell markers at the time the invention was made; as such criteria were known parameters of cell activation." The Examiner also opines that "it was common practice at the time the invention was made to re-activate and re-stimulate cells to maintain proliferation and expansion of cell populations of interest a the time the invention was made" (Office Action, page 4, last paragraph).

Applicants respectfully traverse the Examiner's assertion that the claimed invention would have been obvious to the skilled artisan at the time the invention was made. Reconsideration and withdrawal of this rejection in light of the following arguments is respectfully requested.

Newly added claim 60, and claims depending therefrom, are directed to methods for inducing *ex vivo* proliferation of a population of T cells ***to sufficient numbers for use in therapy*** by contacting said T cells with anti-CD3 and anti-CD28 antibodies ***directly attached to the same surface*** thereby inducing the population of T cells to proliferate to sufficient numbers for use in therapy. As presently claimed, the invention is nonobvious in view of the applied prior art.

To establish a *prima facie* case of obviousness, the Examiner has the burden of showing either that some objective teaching in the prior art or knowledge generally available to one of ordinary skill in the art would have motivated that individual to combine the relevant teachings of the references to arrive at the claimed invention. *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Indeed, the prior art must suggest the combination or convey to those of ordinary skill in the art a reasonable expectation of success of making it. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The teachings of the references can be combined only if there is some suggestion or incentive to do so. *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 221 USPQ 929, 933 (Fed. Cir. 1984). Under section 103, both the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure. *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one of ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. *Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986).

With respect to Ledbetter et al. (EP0440373), Applicants respectfully submit that nowhere in this reference is there a teaching or suggestion to directly attach anti-CD3 antibody or fragments thereof ***and*** anti-CD28 antibody or fragments thereof on the ***same*** surface to induce *ex vivo* proliferation of a population of T cells to sufficient numbers for use in therapy. Moreover, when ***taken as a whole***, this reference teaches away from the claimed invention, as it is directed to "find a novel and efficient method of stimulating T cells to develop ***CD3-independent*** cytolytic activity to attack tumor cells" (see, page 2, ll. 34-35). Thus, one of skill in the art, based on the teachings of this reference would not have been motivated to use a combination of anti-CD3 and anti-

CD28 antibodies, much less directly attach them on the same surface to induce *ex vivo* proliferation of a population of T cells to sufficient numbers for use in therapy.

Ledbetter et al. (U.S. Patent No.: 6,010,902) do not remedy the deficiencies of the primary reference. Instead, this reference amplifies this deficiency by actually teaching away from combining anti-CD3 and anti-CD28 antibodies to stimulate T cells. Specifically, Ledbetter et al. ('902) disclose that CD3/CD28 heteroconjugates comprising monoclonal antibodies G19-4 and 9.3 (column 24, lines 60-62) do not show any significant increase in its ability to activate T cells (as measured by intracellular calcium mobilization) over unstimulated or CD3/CD3-stimulated cells (see column 24, lines 63-67 and column 25, lines 1-34). This is in ***striking contrast*** to the CD3/CD2, CD3/CD4, CD3/CD6 and CD3/CD8 heteroconjugates, ***all of which*** induce a marked increase in calcium mobilization within the T cells treated with those heteroconjugates as compared to the activity of unstimulated or CD3/CD3-stimulated cells (column 25, Table III and lines 25-30). Thus, Ledbetter et al. ***teaches away*** from using anti-CD3 and anti-CD28 to induce T cell proliferation, since the heteroconjugate comprised of anti-CD3 and anti-CD28 antibodies does not stimulate T cell activation over background levels compared to heteroconjugates comprised of other T cell surface marker combinations which support robust activation. Furthermore, even if the CD3/CD28 heteroconjugates or bispecific antibodies of Ledbetter et al. did stimulate T cell activation (which is denied), this would still not render obvious Applicants claimed invention, because heteroconjugates or bispecific antibodies are significantly different to antibodies directly attached to the same surface. Thus, in contrast to the Examiner's assertions, Ledbetter et al. ('902) do not teach stimulating T cells with combination of anti-CD3 and anti-CD28 antibodies, but rather teaches away from using this combination.

Chang (U.S. Patent No.: 6,129,916) also does not remedy the deficiencies of the references discussed above. First, Chang teaches away from *in vitro* methods of activating T cells by teaching that a major concern with ***in vitro*** regimens

> is that the treatment is very tedious, expensive, and requires a sophisticated, specialized cell culture facility. The variation among cells or cultures from different patients requires demanding monitoring procedures. Also, ***lymphocyte cultures have very poor viability even under optimal conditions, meaning that during the culturing, large numbers of the cells will die.*** When large numbers of dead cells are injected into patients, this may actually burden the reticuloendothelial system (RES) and reduce its effectiveness in combating the tumor cells. [***emphasis added***]. See column 3, lines 19-27.

In view of the foregoing teaching by Chang, one of ordinary skill in the art would not have been motivated to activate T cells *in vitro* with the Chang conjugates to induce proliferation of a population of T cells to sufficient numbers for use in therapy as claimed by Applicants.

Chang discloses immunoregulatory conjugates including a polymeric backbone coupled with binding molecules, for example, antibodies which bind to monovalent antigenic epitopes on CD3, epitopes of the T cell receptor, or other antigens on the surface of T cells, e.g., CD2, CD4, CD5, CD8, or CD28 (col. 4, ll. 39-52) or antibodies specific for HLA class I antigens, HLA class II antigens, or anti-CD37 (col. 11, ll. 32-36) for use in activating T cells *in vivo*. There is no teaching or suggestion in Chang that would motivate an ordinary skilled artisan to select the antibodies that bind CD3 and antibodies that bind CD28 among the list of antibodies, which are taught to be equally useful for activating T cells *in vivo*. In fact, based on the teachings of Ledbetter et al. ('902) that CD3/CD28 is ineffective in activating T cells compared to other T cell surface marker combinations (*see*, discussion above), there simply would be no motivation for one of ordinary skill in the art to choose anti-CD3 and CD28 antibodies out of the laundry list of antibodies to T cell surface markers listed in Chang. Additionally, in

light of the data discussed during the Examiner Interview of January 7, 2004, which showed that T cell proliferation is dramatically different depending on which combination of antibodies are attached to the beads that are used to stimulate the T cells (*see*, Appendix A), Applicants respectfully submit that Chang simply did not appreciate these unexpected differences between the different combinations of antibodies in his wish list of antibodies. Chang provides no distinction whatsoever between the antibody combinations he lists with regard to T cell activation. As such, the claims are non-obvious over Ledbetter et al. (US and EP) and Chang.

Thus, Applicants respectfully aver that the proposed combination of references fails to teach or suggest the invention as claimed in the currently pending claims. Moreover, although not acquiescing that the Examiner has established a *prima facie* case of obviousness, as discussed at the January 7, 2004 Examiner's Interview, there is abundant evidence of secondary considerations to support the non-obviousness of the claimed invention.

First, the non-obviousness of the invention is apparent from the results achieved when the invention is put into practice. More specifically, use of the claimed invention as described in the specification, allows for the long-term growth and proliferation of T cells. As demonstrated by Levine, B.L. et al. (1997) *J. Immunol.* **159**:5921-5930 (Appendix B) and Levine, B. L. et al. *Science* **272**(5720):1939-43 (Appendix C) submitted herewith, T cells stimulated with anti-CD3 and anti-CD28 antibodies attached to the same surface pursuant to the teachings of the present invention, remained in exponential proliferation for between 35 to 50 days in culture (Figures 1A and 2A in Appendix B and Fig. 1A in Appendix C). As discussed during the Examiner's Interview, both soluble anti-CD28 antibodies combined with immobilized anti-CD3 antibodies and anti-CD3 and anti-CD28 antibodies attached on separate surfaces are far less efficient, in

stimulating exponential T cell proliferation than anti-CD3 and anti-CD28 antibodies attached on the same surface.

In addition, as discussed during the Examiner's Interview, Applicants have demonstrated that T cells treated *ex vivo* with anti-CD3 and anti-CD28 antibodies attached to the same surface as described in Applicants' specification, exhibit increased cell growth and viability over time as compared to T cells treated using other protocols. A good surrogate for T cell proliferation, and an important property reflecting clinical utility is the survival of the infused T cells in patients after *ex vivo* growth. In independent trials, which were discussed at the Examiner Interview, it was found that T cells treated as taught in Applicants' specification, had high levels of survival of the infused T cells (for example, up to 48 weeks post-infusion compared to 12 weeks of previous approaches). Also, T cells activated as taught by Applicants' specification also maintain the T cell repertoire of the starting T cell population unlike other T cell activation protocols. Additionally, such T cells treated have roughly the same post-thaw viability as pre-freeze viability; this property is especially important when T cells have to be frozen from patients for later use, for instance after chemotherapy.

Furthermore, as discussed with the Examiner during the interview, the claimed invention has received professional approval and achieved commercial and clinical success. In fact, the work reported in the specification and claimed herein has been published in the prestigious journal "Science" (*see*, Appendix C). The work reported in the specification has also been commercialized (the patent application has been licensed to Xcyte Therapies, Inc., Seattle, WA) and is currently being utilized in Phase I and Phase II clinical trials. As discussed at the Examiner's Interview, these clinical trials have shown promising early results. The T cells infused after *ex vivo* activation as claimed herein led to rapid lymphocyte recovery in multiple myeloma and prostate cancer clinical trials. In the multiple myeloma trials, the TCR Vβ skewing seen in

multiple myeloma patients was reduced upon infusion of the T cells activated by the method taught in Applicants' specification and the TCR repertoire was normalized. The T cells produced by the claimed method have also been shown to reduce bone metastases three months after treatment in some patients. Also, in chronic lymphocytic leukemia trials, the enlarged spleen and lymph nodes of patients were reduced in size following infusion of the T cells expanded *ex vivo* as taught by Applicants. In addition, Applicants' methods have also been found to be of potential use in treating head and neck squamous cell carcinomas.

Finally, the significance of Applicants' teachings are also to be found in the numerous instances of others using the methods taught by Applicants' specification to stimulate T cells for use in therapy or (Appendix D provides a few examples: Hellstrom et al. (2001), *Proc. Natl. Acad. Sci. USA* **98**(12):6783-88; Orchard, P.J. et al. (2002) *Hum Gene Ther.* **13**(8):979-88; and Pene J. et al. (2003) *J. Immunol. Methods* **283**:59-66).

For the foregoing reasons, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

IV. Provisional Rejection under the doctrine of obviousness-type double patenting

Claims 50, 53 and 57-58 stand provisionally rejected under the doctrine of obviousness-type double patenting as being unpatentable over copending claims of USSN 08/253,964, USSN 08/592,711, USSN 09/183,055, USSN 09/350,202; and USSN 09/553,865 (Office Action, page 5, paragraph 4).

The Examiner is requested to clarify why a provisional double patenting rejection has been applied over USSN 09/183,055, which is clearly patentably distinct from the claimed invention.

While in no way admitting that claims 50, 53 and 57-58 are obvious over the claims of the other co-pending applications listed above, upon allowance of the claims of these co-pending applications, Applicants will consider submitting a Terminal Disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c), if appropriate, which will obviate this rejection.

V. Rejection under the doctrine of obviousness-type double patenting

Claims 50, 53 and 57-58 stand rejected under the doctrine of obviousness-type double patenting as being unpatentable over claims 1-32 of U.S. Patent No. 6,352,694 (Office Action, page 6, paragraph 6) and over claims 1-29 of U.S. Patent No. 6,534,055 (Office Action, page 6, paragraph 7).

While in no way admitting that claims 50, 53 and 57-58 are obvious over the claims of U.S. Patent No. 6,352,694 and U.S. Patent No. 6,534,055, upon allowance of the claims of the instant application, Applicants will consider submitting a Terminal Disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c), if appropriate, which will obviate this rejection.

V. Conclusion

Applicants believe that all of the outstanding rejections of record have been overcome by amendment and/or argument. Accordingly, the claims are now believed to be in condition for allowance. Applicants respectfully request that the Examiner issue a timely Notice of Allowance.

No fees are believed to be due in connection with this correspondence. If any fees are due, please charge any payments due, or credit any overpayments, to our Deposit Account No. 08-0219.

The Examiner is invited to telephone the undersigned at the telephone number given below in order to expedite the prosecution of the instant application.

Respectfully submitted,

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